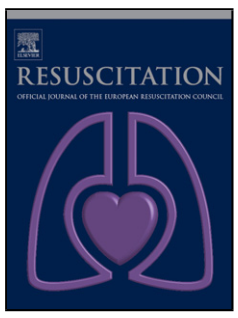

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PII: S0300-9572(19)30080-2
DOI: https://doi.org/10.1016/j.resuscitation.2019.03.014
Reference: RESUS 7952

To appear in: *Resuscitation*

Received date: 9 December 2018
Revised date: 3 March 2019
Accepted date: 6 March 2019

Please cite this article as: Caporro M, Rossetti AO, Seiler A, Kustermann T, Nguepnjo Nguissi NA, Pfeiffer C, Zimmermann R, Haenggi M, Oddo M, De Lucia M, Zubler F, Electromyographic reactivity measured with scalp-EEG contributes to prognostication after cardiac arrest, *Resuscitation* (2019), https://doi.org/10.1016/j.resuscitation.2019.03.014

Electromyographic reactivity measured with scalp-EEG contributes to prognostication after cardiac arrest.

Matteo Caporro[1], Andrea O Rossetti[2], Andrea Seiler[1], Thomas Kustermann[3], Nathalie Ata Nguepnjo Nguissi[3], Christian Pfeiffer[3,4], Rebekka Zimmermann[1], Matthias Haenggi[5], Mauro Oddo[6], Marzia De Lucia[3], Frederic Zubler[1*]

1. Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland.

2. Department of Neurology, University Hospital (CHUV) & University of Lausanne, Switzerland.

3. Laboratoire de Recherche en Neuroimagerie (LREN), University Hospital (CHUV) & University of Lausanne, Switzerland.

4. Department of Psychology, University of Zürich, Switzerland.

5. Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland.

6. Department of Intensive Care Medicine, University Hospital (CHUV) & University of Lausanne, Switzerland.

Corresponding Author (*)
Frederic Zubler, MD, PhD
Sleep-Wake-Epilepsy-Center
Department of Neurology
Bern University Hospital - Inselspital Bern
Freiburgstrasse 4
3010 Bern
Switzerland
E-mail: frederic.zubler@gmail.com

Words in the Abstract:	168 words
Words in the main text:	2964 words
Figures:	1
Tables:	3

Abstract

Aim: To assess whether stimulus-induced modifications of electromyographic activity observed on scalp EEG have a prognostic value in comatose patients after cardiac arrest.

Methods: 184 adult patients from a multi-centric prospective register who underwent an early EEG after cardiac arrest were included. Auditory and somatosensory stimulation was performed during EEG-recording. EEG reactivity (EEG-R) and EMG reactivity (EMG-R) were retrospectively assessed visually by board-certified electroencephalographers, and compared with clinical outcome (cerebral performance category, CPC) at three months. A favorable functional outcome was defined as CPC 1-2, an unfavorable outcome as CPC 3-5.

Results: Both EEG-R and EMG-R were predictors for good outcome (EEG-R: accuracy 72% (95%-CI: 66-79), sensitivity 86% (78-93), specificity 60% (50-69); EMG-R: accuracy 65% (58-72), sensitivity 61% (51-75), specificity 69% (60-78)). When reactivity was defined as EEG-R and/or EMG-R, the accuracy was 73% (67-70), the sensitivity 94% (90-99), and the specificity 53% (43-63).

Conclusion: Taking EMG into account when assessing reactivity of EEG seems to reduce false negative predictions for identifying patients with favorable outcome after cardiac arrest.

Keywords: cardiac arrest; coma; prognostication; EEG; EMG; reactivity

1. Introduction

Prognostication in comatose patients after cardiac arrest (CA) remains a challenging task for clinicians in the intensive care unit [1]. One of the main diagnostic and prognostic tools is the electroencephalogram (EEG). While the vast majority of existing prognostic modalities target identification of subjects with poor outcome [1], several EEG features have been shown to be associated with either favorable or unfavorable outcome. EEG reactivity (EEG-R), namely the modification of EEG background following external stimulation, has been recognized as a predictor for good prognosis in comatose patients at the intensive care unit [2,3], in particular for patients with hypoxic/anoxic encephalopathy after CA [4–9]. There is however no uniform definition of EEG-R. For instance, recommendations of the American Clinical Neurophysiology Society define reactivity as a "change in cerebral EEG activity to stimulation (...), [which] may include change in amplitude or frequency, including attenuation of activity" [10]. By contrast, appearance of rhythmic or periodic patterns after stimulation ("SIRPIDs") is considered a predictor for poor functional outcome [11].

Besides cerebral activity, scalp-EEG electrodes often register electromyogram (EMG) activity, especially on the frontal and temporal regions - due to the tonic and phasic contraction of the frontal and temporal muscles [12]. Usually, electromyographic reactivity (EMG-R), that is modifications of the muscle activity after stimulus, is not taken into account in the definition of reactivity [10]. This point was explicitly addressed in a recent consensus survey, in which 88% of the 24 international EEG experts who participated declared that EMG-R should not qualify as EEG reactivity [3]. Currently, EMG activity in comatose patients after CA is rather considered as an artifact, that if too abundant may be suppressed pharmacologically [13] or with computational methods [14] to ensure better interpretation of the EEG.

However, muscle activity is regulated by the central nervous system, and varies with different vigilance states, both in physiological and pathological conditions; for example muscle atonia is a hallmark of Rapid-Eye-Movement sleep [15]. Motor response to pain (visually assessed, for instance within the Glasgow Coma Scale) is a

predictor for outcome after CA [16]. Frontalis EMG was used for arousal detection during general anesthesia [17], and currently several proprietary algorithms for monitoring sedation depth based on EEG incorporate high frequencies (> 30Hz) [18] , which on the scalp mainly correspond to muscle activity.

In this paper, we systematically investigate the prognostic value of EMG-R observed during scalp-EEG, either isolated or in conjunction with EEG-R, for identifying patients with good outcome in the early phase after cardiac arrest.

2. Methods

Patients and treatment

Patients were recruited in the Intensive Care Department of two university hospitals in Switzerland, in Lausanne (Centre Hospitalier Universitaire Vaudois) and Bern (Inselspital). The cohort was part of a prospective multi-centric register [4]. The study protocol was approved by the ethical commissions of each hospital (number VD-116/13). For the present study, we included comatose patients after cardiac arrest (CA) who underwent an EEG during controlled normothermia (CNT) at 36°C. The recruitment period in Lausanne was from January 2015 (establishment of controlled normothermia) until March 2017; since recruitment in Bern started later (June 2016), we extended the recruitment period for 6 months (until September 2017). Recruitment periods were determined before start of the analysis.

CNT was performed using ice packs or intravenous ice-cold fluids together with a feedback controlled cooling device (Arctic Sun System, Medivance, Louisville or Thermogard XP, ZOLL Medical, Zug, Switzerland) for 24h. During CNT either propofol (4 mg/kg/h) or midazolam (0.1 mg/kg/h) and fentanyl (1.5 μg/kg/h) were given for analgesia and sedation, and vecuronium, rocuronium, or atracurium for controlling shivering if needed. In Lausanne, three patients were given myorelaxants during EEG recording to reduce artifacts.

Decision to remove life supporting treatment was taken 72h after CA or later, if two of the following criteria were met 1) unreactive EEG background in a recording

performed at least 36h after CNT and off sedation, 2) treatment-resistant myoclonus, 3) bilateral absence of N20 in SSEP, 4) incomplete return of brainstem reflexes [4]. In Bern, an additional criteria for withdrawal of intensive care support was the association of extensive hypoxic/ischemic lesions on the MR-scan with a serum neuron-specific enolase level twice above 33 µg/l.

The clinical outcome was prospectively assessed with the Cerebral Performance Category (CPC) [19] at three months, by phone interview. A CPC value of 1 (no deficits) or 2 (minor deficits) was considered as a favorable outcome, whereas a CPC of 3 (severe deficits), 4 (vegetative state) or 5 (death) was considered an unfavorable outcome).

EEG recordings

All EEGs were performed during CNT. At the Lausanne University Hospital, Video-EEG (Viasys Neurocare, Madison, WI) recordings were performed for 20–30 min with 19 electrodes according to the international 10-20 system, with reference placed near FpZ. The sampling rate was usually 250Hz, in a few cases 1000 Hz. Recordings were available to treating clinicians for detection and treatment of epileptic seizures, but were not taken into account for the decision to continue or withdraw treatment on the third day. At the Bern University Hospitals EEGs were performed at 1200 Hz using a 63 active ring electrode array (g.HIamp, g.tec medical engineering, Graz, Austria) using the 10-10 system, referencing to the right ear lobe. Only the electrodes from the 10-20 system were considered in the present study. Recordings in Bern were performed in the context of a research project involving a mismatch negativity paradigm [20,21], after which 10 minutes of baseline EEG and then EEG during stimulations were recorded. Traces were not available to treating clinicians, however a minority of patients underwent an additional EEG shortly before or after the study EEG in case of clinical suspicion of seizures.

Stimulation and reactivity

Stimulation was performed with repetitive auditory stimuli (usually calling the patient's name, then hand clapping) and somatosensory stimuli (combining peripheral stimuli such as finger nail compression, and central stimuli such as bilateral nipple pinching or sternum friction) by a certified EEG-technician (Lausanne), or a board-

certified neurologist (Bern). Passive eye opening was not taken into account for determining reactivity, as this procedure was not systematically performed on all patients. In both centers, beginning and end of stimulus (lasting from 1 to several seconds) was marked during the recording.

Three board-certified electroencephalographers (MC, AS, and FZ) blind to clinical outcome performed the visual analysis for reactivity retrospectively. By default, a 4^{th} order Butterworth band-pass filter between 0.5 and 70 Hz was applied, and the EEG-traces were displayed on 10-second epochs using a longitudinal bipolar montage. However, the examiners were allowed to modify the settings if desired, and were free to use a notch filter 48-52 Hz. EEG-R was defined as a clear modification of the amplitude and/or the frequency of the EEG background occurring during or at most 3 seconds after the application of the stimulus. Appearance or modification of periodic or rhythmic patterns, as defined by the ACNS guidelines [10], in absence of background modification, was not considered as EEG-R. EMG-reactivity (EMG-R) was defined as a clear modification of amplitude of the muscle activity, or of the number of channels on which muscle activity was seen. To enforce these criteria, examiners were not asked to judge the presence or absence of reactivity, but to report separately the effect of auditory and of somatosensory stimulus on 1) the amplitude of EEG background, 2) the frequency of EEG background and 3) the EMG activity using the categories increase, decrease or no modification clearly attributable to stimuli. Each recording was analyzed independently by two examiners (each examiner was attributed randomly 2/3 of recordings); in case of disagreement, a consensus was reached and/or the opinion of the third examiner was required.

In addition, background EEG continuity was visually assessed according to [10]. In particular, we considered two sub-groups of EEG patterns. Firstly, with either a continuously suppressed background (with or without superimposed periodic patterns) or a burst-suppression (defined as >50% of the traces <10 μ V). In accordance with the terminology introduced by Westhall et al [22], we called this sub-group “highly malignant pattern” (even though the original description was made in recordings performed at least 72h after CA). Secondly, the sub-group consisting of EEGs with continuous background or only stimulus-induced suppression/attenuation.

Statistics

The primary goal of this study was to compare the sensitivity and specificity for good outcome of reactivity defined as a modification of EEG background (EEG-R) versus reactivity defined as a modification of EEG background and/or modification of EMG activity (EEG-R and/or EMG-R). Differences in sensitivity and specificity were assessed with a McNemar test (performed on patients with favorable outcome and unfavorable outcome, respectively). Pairwise agreement between examiners was assessed with Cohen's κ, whereby only the presence (and not the type) of modifications was considered. For patients' demographics, differences between groups were assessed with Mann-Whitney-U tests for numerical values and with Chi-square tests for categorical data. Statistical analysis was performed with the Machine Learning and Statistics Toolbox from Matlab R2017a (Version 9.2, Matworks, Natwick, MA) for Mann-Whitney-U and Chi-square tests, and with SPSS (Version 25, IBM, Armonk, NY) for McNemar's test and Cohen's κ.

3. Results

During the recruitment period, 144 patients from Lausanne and 40 patients from Bern were included (total 184, 45 women). The mean age (± SD) was 63.4 (± 15.0) years. 90 patients had favorable, and 94 patients unfavorable outcome at three months (of which 82 died). All EEGs were recorded during CNT; the mean latency was 21 (±7) hours after CA. The patients' demographics are shown in Table 1.

115 recordings showed EEG reactivity (EEG-R); 84 recordings showed EMG reactivity (EMG-R), from which 70 with presence of EEG-R and 14 in absence of EEG-R (typical examples are presented in Figure 1); 129 recordings showed at least one type of reactivity (EEG- and/or EMG-R). The inter-rater agreement for EEG-R was 87% (κ: 74), for EMG-R 83% (κ: 65). The resulting inter-rater agreement for reactivity defined as EEG- and/or EMG-R was 91% (κ: 78).

The performance of the different types of reactivity for predicting clinical outcome is presented in Table 2. As expected, EEG-R was a predictor for favorable outcome,

whereby the sensitivity was higher than the specificity. EMG-R alone was also a predictor for favorable outcome, however the accuracy was slightly lower. Finally, combining EEG-R and/or EMG-R lead to a significant increase of sensitivity compared to EEG-R alone (94% vs. 86%, p = 0.008, McNemar), at the cost of a lower specificity (53% vs. 60%, p=0.03, McNemar). Accordingly, the negative predictive value (NPV) increased from 81% to 91% (whereas accuracy and positive predictive value were not affected).

Combining background reactivity and continuity

Table 3 shows the influence of EMG-R when reactivity was associated to background EEG continuity for prognostication. A continuous background was often associated with favorable outcome; however, the sensitivity was low. Also considering EEG-R as marker for favorable outcome (continuous background and/or EEG-R) considerably increased the sensitivity; including EMG into the definition of reactivity further increased it.

Burst-suppression and a continuously suppressed background, collectively referred to as "highly malignant pattern", were both strongly associated with unfavorable outcome. However, six patients with burst suppression had a favorable outcome. All six had non-identical bursts (as defined in [23]) and no highly epileptiform bursts [10] - and all showed one type of reactivity (two had EEG-R and the remaining four had EMG-R; no patient showed both reactivities). As such, adding the absence of reactivity as necessary criterion increased the specificity for unfavorable outcome from 93% to 96% for EEG-R, and to 100% for EEG-R and EMG-R.

4. Discussion

This retrospective analysis of prospectively collected EEG in comatose patients after CA shows that taking changes of muscle activity into account when judging reactivity of an EEG trace increased significantly the sensitivity for good outcome.

Currently, most guidelines recommend to discard muscle activity when judging reactivity on scalp EEG [10,16], However we show, to the best of our knowledge for

the first time, that EMG-R can contribute meaningfully to prognostication after cardiac arrest. When considered alone, changes in EMG activity after stimulus correctly predicted the outcome for about two-thirds of patients. The benefit of EMG-R was greater when combined with "classical" EEG-R.

These results are of relevance for clinicians confronted with the decision to continue or withdraw intensive care support in comatose patients after CA. For outcome prediction based on reactivity, consequences of a false negative (falsely predicting that a patient will not have a favorable outcome, when he actually would) are undoubtedly more harmful than a false positive (falsely predicting good outcome for a patient who in fact will have a poor functional outcome). Using EEG and/or EMG-R instead of EEG-R alone reduced the percentage of errors (false negatives) in patients with absence of reactivity from 19 % to 9 % (1-NPV).

Also when reactivity was combined with another important feature of EEG analysis, namely background continuity, inclusion of EMG-R could reduce false negatives for detecting favorable outcome (or false positives for detecting unfavorable outcome).

Physiological and practical aspects of EMG-R

Several mechanisms might explain why EMG-R brings additional information to EEG-R when interpreting reactivity. One obvious reason is that the presence of EMG activity can impair EEG interpretation ("muscle artifacts"). In these cases, judging reactivity on EMG increases the signal-to-noise ratio. Conversely, EMG-R is difficult to assess when very little EMG activity is present, a situation which usually improves the EEG readability. Because of this complementarity and conflicting requirements for EEG- or EMG-quality, examiners in this study disagreed on both EEG-R and EMG-R in only 4 subjects.

We also observed that the EMG baseline (that is, in absence of stimulation) was often more stable than the EEG baseline. Moreover, stimulus-induced EMG-modifications lasted often longer than EEG-modifications. This point is illustrated in Figure 1a: it is possible that the nociceptive stimulus did induce a flattening of the EEG, but this flattening was also observed every few seconds during baseline condition (discontinuous EEG). By contrast, in the same example, EMG activity was not

present before the stimulus, and persisted for almost one minute after the stimulus. EEG background can also be difficult to assess for other reasons, for instance in presence of periodic patterns or epileptiform activity (Figure 1b).

EEG-R contributes to prognostication by assessing afferent (sensory) pathways, thalamic relays and the cerebral cortex [24]. By contrast, EMG-R does not necessarily require cortical activation, but requires functional efferent pathways at the brain stem level (cranial nerves V and VII for temporal and frontal muscles, respectively). One can postulate that in a few cases in which the cortical activity was still recovering after the anoxic-ischemic phase, or still severely impaired by sedation during CNT, EMG-R could help identify patients with a still functioning brainstem.

Strengths and limitations

We investigated a relatively large number of patients from a prospectively acquired and well characterized multi-centric cohort. Each stimulus modality was performed at least twice. The requirement to describe specifically the effect of stimulation on amplitude and frequency of EEG activity resulted in a high inter-rater agreement, which was comparable to or higher than in previous studies [25,26]. The transposition to "real-world" conditions is supported by the fact that no patient was excluded due to EEG artifacts.

In this study we analyzed early EEGs performed during CNT. The reasons are, first, that early EEGs seem to have a better predictive value for good outcome [9,27], and second, that these EEGs were not taken into account for the final decision to continue or withdraw intensive care support. However, the timing of the EEG varied between 5 and 30 hours after CA. This constitutes a limitation, as EEGs are known to vary during the first 30 hours after CA [9,28]. In particular, burst-suppression [28] or a suppressed background [9] can be observed early even in patients with favorable functional outcome, whereas at 72h after CA and after rewarming they are more specifically associated with unfavorable outcome [22,29]. In our cohort, no patient with suppressed background had a favorable outcome, as opposed to six patients with burst-suppression. It is known, however, that burst-suppression is a heterogeneous group (subcategories are for instance burst-suppression with or without identical bursts [23], highly epileptiform vs. not highly epileptiform bursts [10]). Our results

suggest that a combination of EEG-R and EMG-R can help reduce false positive prediction of poor prognosis in case of early burst-suppression without identical or highly epileptiform bursts (a pattern possibly due to early EEG, or to sedation). Follow-up studies are needed to better assess the benefit of EMG-R for prognostication at 72h after CA.

A limitation of our study is that the administration or not of myorelaxants could only be retrieved in 144/184 patients, but since myorelaxants were administrated in a minority of patients during CNT (<10 %) this factor is unlikely to represent a relevant bias. As a surrogate we analyzed the proportion of patients with baseline EMG activity (prior to stimulation), which was not significantly different between patients with favorable or unfavorable outcome. Another possible limitation of our study is that visual stimuli were not taken into account, since it was not routinely performed in Bern; moreover stimulations in Bern were not always performed in the same standardized way than in Lausanne [30]. Finally, we only combined reactivity with one other aspect of EEG background, namely continuity. The additional value of EMG-R compared to EEG-R alone in relation to other elements of EEG analysis remains to be investigated.

Conclusion and outlook

Based on the results of our study, we propose that EMG should be considered in the assessment of reactivity. In particular in cases where EEG-R was difficult to interpret due to artifacts or non-stationarity, EMG-R could help reduce false negative for good outcome. However, our study was conducted on EEGs recorded early and within a relatively large time-window. Whether the complementarity of EMG-R and EEG-R holds 72h after CA and in absence of sedation remains to be confirmed.

Author contributions

MC, AOR, RZ, FZ designed the study; AOR, TK, NANN, CP, RZ, MH, MDL, FZ acquired the data; MC, AS, FZ analyzed the data; all authors drafted the paper and took responsibility for the final version

Funding

FZ was supported by the Baasch-Medicus Foundation. The Swiss National Foundations provided financial support to AOR (CR3213_143780) and to MO (32003B_155957). MDL was supported by EUREKA-Eurostars, Grant Number E 9361 Com-Alert.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgement

The authors thank Kaspar Schindler for helpful comments, and Christine Staehli, Jan Novy, and Daria Solari for help in collecting the data.

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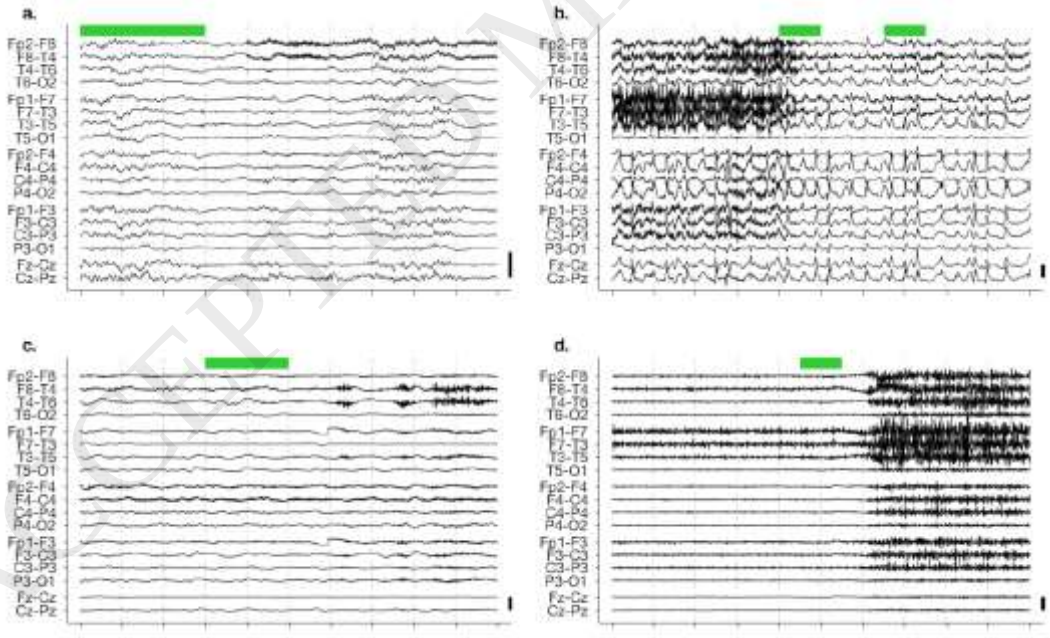
Figure

Figure 1: Examples of electromyographic reactivity (EMG-R) in absence of clear electroencephalographic reactivity (EEG-R). Longitudinal bipolar montage, 10-second epochs, vertical bar = 100 μV. Timing of stimuli application is marked in green. (a) EEG of a 66-year old male, favorable outcome (CPC 1), recorded 19 h after CA. Appearance of muscle activity mainly on right frontal regions after release of a peripheric somatosensory stimulus (finger pinching) applied for about 7 seconds, discontinuous EEG without clear modification following stimulation. (b) EEG of a 42-year old female, favorable outcome (CPC 2), recorded 26 h after CA. Clear reduction in tonic muscle activity after auditory stimulus (2 x call of patients name). The epileptiform activity prevents clear appreciation of EEG background reactivity. (c) EEG of a 73-year old female, favorable outcome (CPC 2), recorded 28 h after CA. Despite bolus of tracrium before recording a clear increase of muscle activity in response to finger pinching is seen (d) EEG of a 60 year old male, unfavorable outcome (CPC 5), recorded 14 h after CA. Increase of tonic muscle activity after auditory stimulus (hand clapping) over a suppressed EEG.



Tables

Table 1: Patients demographics. 1) Continuous background or only stimulus-induced discontinuities (categories a or b1 according to [10]). 2) as defined in [22]. 3) Documented only for 144 patients.

	Favorable outcome	Unfavorable outcome	p-value
N	90	94	n.a.
Female	16 (18%)	29 (31%)	0.039
Age (±SD) [y]	61.3 (± 14.2)	65.6 (±15.5)	0.025
Non-cardiac etiology	12 (13%)	31 (33%)	0.0016
Asystole or pulseless electrical activity on site	18 (20%)	58 (62%)	<0.001
Latency of EEG recording (±SD) [h]	20.5 (±6.3)	21.9 (±7.6)	0.22
Continuous EEGs[1]	43 (48%)	18 (19%)	< 0.001
"highly malignant pattern" [2] [suppressed/burst-suppression]	6 (7%) [0/6]	50 (53%) [17/33]	< 0.001
Baseline EMG activity present	54 (60%)	47 (50%)	0.17
Patients sedated with propofol	49 (54%)	39 (41%)	0.08
Propofol dosis (±SD) [mg/kg/h]	2.3 (±1.1)	2.2 (±1.3)	0.36
Patients sedated with midazolam	32 (36%)	25 (27%)	0.19
Midazomal dosis (±SD) [mg/kg/h]	0.13 (±0.06)	0.10 (±0.05)	0.16
Patients sedated with fentanyl	56 (62%)	44 (47%)	0.05
Fentanyl dosis(±SD) [mg/kg/h]	1.15 (±0.7)	1.20 (±0.9)	0.75
Patients with myorelaxants[3]	6/69 (9%)	5/75 (7%)	0.65

Table 2: Performance of reactivity for predicting favorable outcome (EEG-R, modification of EEG background after stimulus; EMG-R: modification of EMG activity after stimulus; EEG- and/or EMG-R: modification of EEG background and or EMG activity; 95% CI, 95%-confidence interval; PPV, positive predictive value; NPV, negative predictive value).

Favorable outcome	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
EEG-R	72% (66-79)	86% (78-93)	60% (50-69)	67% (58-76)	81% (72-90)
EMG-R	65% (58-72)	61% (51-71)	69% (60-78)	65% (55-76)	65% (56-74)
EEG- and/or EMG-R	73% (67-80)	94% (90-99)	53% (43-63)	66% (58-74)	91% (83-99)

Table 3: Combining EEG background reactivity and continuity for predicting favorable or unfavorable outcome (95% CI: 95%-confidence interval; EEG-R: modification of EEG background after stimulus; EMG-R: modification of EMG activity after stimulus; highly malignant pattern: burst-suppression or suppressed background; PPV: positive predictive value; NPV: negative predictive value).

Favorable outcome	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Continuous background	65% (58-72)	48% (37-58)	81% (73-89)	70% (59-82)	62% (53-70)
Continuous background or EEG-R	73% (67-80)	91% (85-97)	56% (46-66)	67% (58-75)	87% (78-95)
Continuous background or EMG-R	69% (62-76)	74% (65-83)	64% (54-74)	66% (57-76)	72% (63-82)
Continuous background or EEG-R or EMG-R	73% (67-80)	97% (93-100)	51% (41-61)	65% (57-73)	94% (88-100)
Unfavorable outcome	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Highly malignant pattern	73% (66-79)	53% (43-63)	93% (88-99)	89% (81-97)	66% (57-74)
Highly malignant pattern without EEG-R	72% (66-79)	50% (40-60)	96% (91-100)	92% (85-100)	65% (57-73)
Highly malignant pattern without EMG-R	71% (65-78)	46% (36-56)	98% (95-100)	96% (90-100)	63% (55-71)
Highly malignant pattern without EEG-R or EMG-R	72% (65-78)	45% (35-55)	100% (100-100)	100% (100-100)	63% (55-71)